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Novel electrocardiographic features in carriers of hypertrophic cardiomyopathy causing sarcomeric mutations

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ABSTRACT

Objectives: The sensitivity and specificity of the conventional 12-lead ECG to identify carriers of hypertrophic cardiomyopathy (HCM) – causing mutations without left ventricular hypertrophy (LVH) has been limited. We assessed the ability of novel electrocardiographic parameters to improve the detection of HCM mutation carriers. **Methods:** We studied 140 carriers (G+) of the *TPM1*-Asp175Asn or *MYBPC3*-Gln1061X pathogenic variants for HCM: The G+/LVH+ group ($n = 98$) consisted of mutation carriers with LVH and the G+/LVH− group ($n = 42$) without LVH. The control group consisted of 30 subjects. The standard 12-lead ECG was comprehensively analyzed and two novel ECG variables were introduced: RV1<RV2>RV3 and septal remodeling. A subset of 65 individuals underwent cardiac magnetic resonance imaging and 2D strain echocardiography.

Results: Conventional major ECG criteria were sensitive (90%) and specific (97%) in identifying G+/LVH+ subjects. RV1<RV2>RV3 and septal remodeling were more prevalent in the G+/LVH− subjects compared to the control group (33% vs 3%, $p = 0.005$ and 45% vs 3%, $p < 0.001$, respectively). The combination of RV1<RV2>RV3 and Q waves and repolarization abnormalities (QR) differentiated between the G+/LVH− subjects and the control group with a sensitivity of 52% and specificity of 97%. The combination of septal remodeling and QR differentiated between G+/LVH− subjects and the control group with a sensitivity of 64% and specificity of 97%.

Conclusions: The novel ECG-parameters RV1<RV2>RV3 and septal remodeling were effective in identifying G+/LVH− subjects and could be useful in the diagnostics of new suspected HCM patients and in the screening and follow-up of HCM families.

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease and one of the leading causes of sudden cardiac death in young people and competitive athletes [1]. To date, over 1500 pathological gene variants in eight genes encoding sarcomeric proteins have been found [2]. In probands with clinical HCM, however, a pathogenic variant is identified in approximately 30–60% of cases [2,3]. The diagnostic accuracy of identifying individuals at risk for

developing HCM in families of probands with no identified variant needs improvement. Disease development in carriers of pathogenic variants without LVH (G+/LVH−) should also be monitored regularly [3]. The standard 12-lead electrocardiogram (ECG) is an inexpensive and universally available method used widely in the diagnostics of HCM. Common ECG findings in HCM include LVH, abnormal Q waves and repolarization abnormalities such as T-wave inversions, ST-segment depression, and prolonged QT [4–8]. However, the sensitivity and specificity of the ECG to identify G+/LVH− subjects have been limited and the prior published data are scarce [4,5,8–10]. In this study our objective was to investigate previously unreported ECG abnormalities of R-wave amplitude distribution and QRS configuration in leads V1–V3 to identify carriers of a pathogenic HCM variant with or without

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echocardiographic LVH. In addition, we aimed to correlate the ECG findings of mutation carriers with comprehensive imaging data in a subset of 65 subjects.

Material and methods

Patients

The patients were recruited from families with HCM evaluated at Kuopio and Helsinki University Hospitals and the Central Hospital of Central Finland. The study population consisted of 140 subjects carrying either one of two Finnish founder mutations causing HCM: The Gln1061X mutation in *MYBPC3* or the Asp175Asn mutation in *TPM1*. Mutation carriers with documented maximum LV wall thickness (MWT) ≥ 13 mm on echocardiography comprised the G+/LVH+ group ($n = 98$). Mutation carriers without the HCM phenotype (MWT < 13 mm) were classified as the G+/LVH− group ($n = 42$). The control group ($n = 30$) consisted of relatives of individuals with either one of the two variants, with a structurally normal heart by echocardiography and who were not carriers of the two studied variants. The Ethics Committees at the Kuopio and Helsinki University Hospitals approved the study protocol. The study conforms to the principles outlined in the Declaration of Helsinki.

Laboratory methods

Venous blood samples were collected and the plasma concentrations of the N-terminal portion of brain natriuretic peptide (NT-proBNP) were determined with immunoassays utilizing antisera directed to NT-proBNP. The sensitivity of the assay was 40 pmol/L. The genetic studies were performed in the Genome Center of Eastern Finland, as previously described [11].

ECG analysis

All standard 12-lead ECGs, recorded at 50 mm/s speed and 10 mm/mV gain, were analyzed manually by one investigator (KN) blinded to the clinical data. The amplitudes of the R and S waves were measured from all the 12 standard ECG leads. The ST segment was considered elevated or depressed if it was 0.5 mm or more above or below the baseline, respectively, determined by drawing a line between subsequent PR intervals. The T wave was considered negative if it was 1 mm or more below the baseline. We did not include patients with left bundle branch block or pacemaker ECG.

In addition to the amplitudes of the R and S waves in all the 12 ECG leads, the following previously described ECG parameters were recorded: 1) pathological Q waves: any Q wave ≥ 40 ms in duration, or ≥ 3 mm deep, or Q/R-ratio ≥ 0.25 , in ≥ 2 contiguous leads except lead aVR [12], 2) absence of normal Q wave in V5–V6 [13], 3) highest R wave in the precordial leads outside of leads V4–V6 [14], 4) LVH according to the Sokolow-Lyon criteria (SV1 + maximal R wave amplitude of V5 or V6 ≥ 35 mm), 5) LVH according to the Cornell voltage-duration product defined as: QRS-duration (ms) \times (RaVL [mm] + SV3 [mm]). For women +8 mm was added to the voltage. The product was positive for LVH with a cutoff of ≥ 2440 [15], 6) QRS duration > 100 ms, 7) RI+SIII > 25 mm [16], 8) RI+SIII-RIII-SI > 17 mm [17], 9) S $>$ R in V4 [18], 10) Romhilt-Estes point score ≥ 4 suggesting LVH [19], 11) P-terminal force (PTF; negative portion of the P-wave in lead V1 ≥ 0.04 mm·s), 12) ST-segment depression ≥ 0.5 mm in ≥ 2 contiguous leads, 13) T-wave inversion ≥ 1 mm in ≥ 2 contiguous leads, except for leads aVR and V1, 14) frontal plane left, right or superior axis deviation, 15) fragmented QRS (as defined by Das and Zipes) [20], 16) poor R-wave progression (PRWP) [21], or 17) reverse R-wave progression in leads V1–V3 [21], 18) rhythm other than sinus, 19) prolonged PR interval, 20) prolonged QTc interval ≥ 440 ms (Bazett formula).

The electrocardiographic parameters proposed by McKenna et al. were considered as major criteria for HCM detection, including pathological Q waves, LVH by Romhilt-Estes score ≥ 4 , and T-wave inversion (> 3 mm) in at least two leads [22]. Composite ECG criteria were analyzed to aid in clinical identification of G+/LVH+ and LVH− subjects (Table 1): Q waves and repolarization abnormalities (QR; repolarization abnormalities = T-wave inversion and/or ST-segment depression and/or prolonged QTc) and hypertrophy by Cornell voltage-duration product and/or Sokolow-Lyon criteria and/or Romhilt-Estes score ≥ 4 .

In addition, we studied two novel ECG parameters. First, RV1<RV2>RV3, defined as the R wave peak being higher in V2 compared to V1 and V3 (Fig. 1), which we decided to include based on experience from clinical practice and from pathophysiological processes involved in HCM. Second, a composite ECG criterion named septal remodeling was analyzed, which we have previously used in a study on dilated cardiomyopathy [23]. Septal remodeling was positive with at least one of the following findings in the leads V1–V3: (1) pathological Q waves in ≥ 2 contiguous leads, (2) QRS fragmentation in ≥ 2 leads, (3) PRWP accompanied by QRS fragmentation, or (4) disorderly distributed R-wave amplitudes, either RV2>RV3 or RV1>RV2. The possibility of lead switch was searched for by analyzing the morphology of the P and S waves in the precordial leads; no suspicious cases were observed.

Echocardiography

All subjects underwent conventional echocardiographic assessment with emphasis on changes due to HCM. Measurements were made according to ACC/AHA/ASE guidelines. MWT was measured from 2D images with optimal beam alignment to the interrogated wall.

Table 1
Baseline variables of the study groups.

	Control (n = 30)	G+/LVH− (n = 42)	G+/LVH+ (n = 98)	p-Value
Baseline				
Female	70% (21)	62% (26)	40% (39)*,†	0.004
Age	42 \pm 16	33 \pm 15	48 \pm 14†	<0.001
Pathogenic variant				
MYBPC3-Gln1061X		88% (37)	62% (61)	
TPM-Asp175Asn		12% (5)	38% (37)	
NYHA				0.003
I		98% (41)	78% (76)	
II		2% (1)	21% (21)	
III			1% (1)	
Atrial fibrillation		0	9% (9)	0.031
RBBB			3% (3)	
IVCD			2% (2)	
ICD			3% (3)	
Betablocker		7% (3)	23% (23)	
ACEi/ARB		2% (1)	22% (22)	
Echocardiography				
LVEF (%)	62 \pm 6	63 \pm 6	63 \pm 10	0.741
MWT (mm)	10.2 \pm 1.1	9.9 \pm 1.4	18.7 \pm 4.5*,†	<0.001
SWT (mm)	9.2 \pm 1.4	9.6 \pm 1.5	16.8 \pm 4.0*,†	<0.001
PWT (mm)	9.1 \pm 1.5	8.5 \pm 1.2	10.4 \pm 1.9*,†	<0.001
SWT/PWT	1.0 \pm 0.1	1.1 \pm 0.2	1.6 \pm 0.4*,†	<0.001
LVEDD (mm)	48 \pm 5	46 \pm 4	46 \pm 6	0.152
LAD (mm)	33 \pm 4	33 \pm 5	41 \pm 7*,†	<0.001

Presented as mean \pm SD or percentage and number of subjects in parentheses. ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ICD = implantable cardioverter defibrillator, IVCD = intraventricular conduction delay, LAD = left atrial dimension, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, MWT = maximal wall thickness, SWT = septal wall thickness, PWT = posterior wall thickness, RBBB = right bundle branch block, SWT/PWT = septal to posterior wall thickness ratio.

* p < 0.05 for difference between indicated group and control group.

† p < 0.05 for difference between G+/LVH+ and G+/LVH− groups.

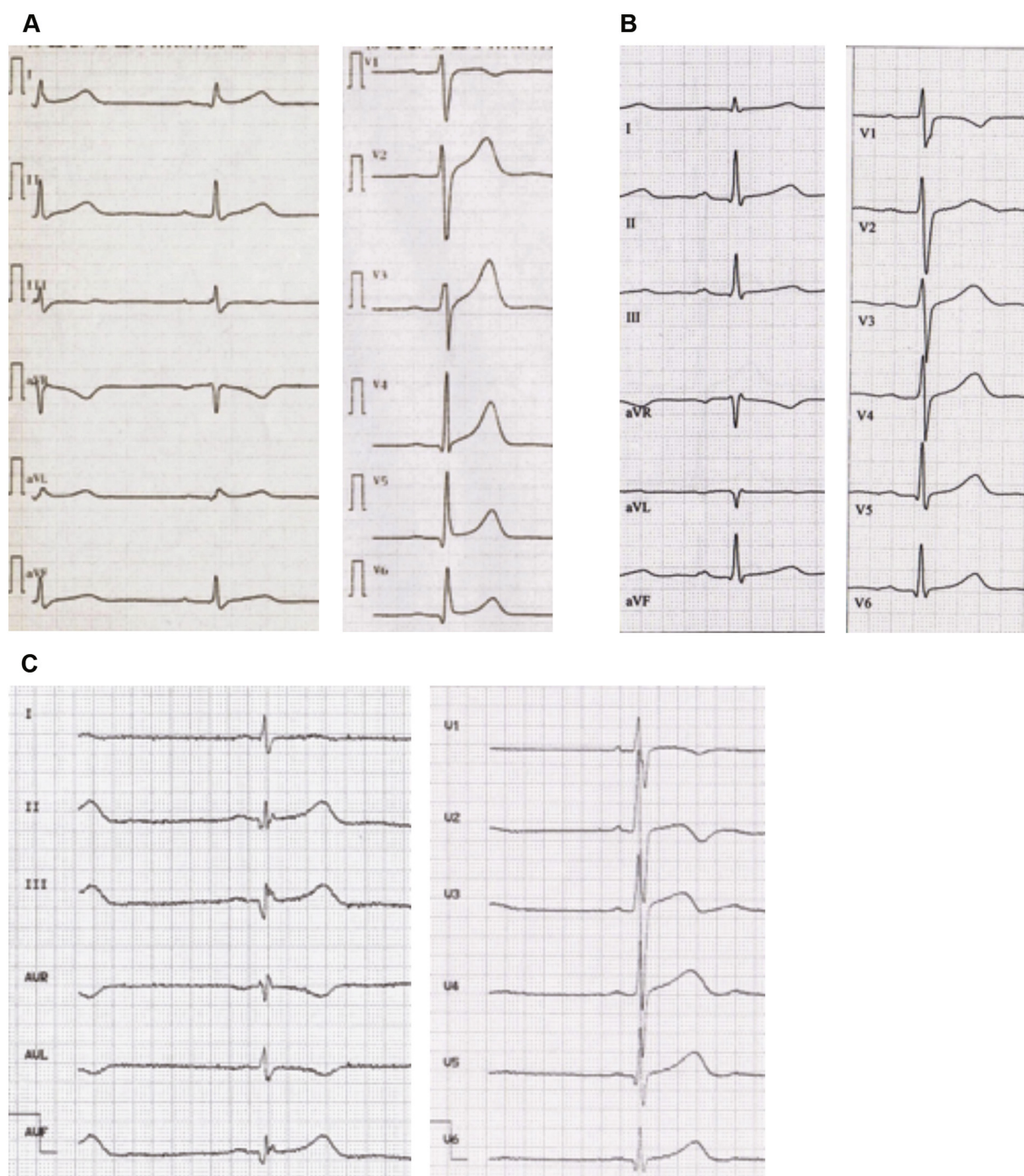


Fig. 1. A) The ECG of a 23 y old male with a pathogenic *MYBPC3* variant without echocardiographic left ventricular hypertrophy. The R wave in lead V2 is higher than in lead V1 and V3 (RV1<RV2>RV3 sign). B) The ECG of an 18 y old female with a pathogenic *MYBPC3* variant without echocardiographic left ventricular hypertrophy. The R wave in lead V2 is higher than in lead V1 and V3 (RV1<RV2>RV3 sign). In addition, the R-wave in lead V1 is higher than the R-wave in lead V3. C) An 18-year old male with a pathogenic *MYBPC3* variant and increased septal thickness of 18 mm. The ECG shows the RV1<RV2>RV3 pattern. The R-waves are relatively low in the leads V5 and V6 with a pathological Q/R ratio in lead V6. In addition, there are Q waves and fragmented QRS complexes in II, III, and aVF, and inverted T-waves in aVL and V2. The Cornell left ventricular hypertrophy criteria are fulfilled.

Imaging substudy

Comprehensive cardiac magnetic resonance imaging (CMRI) and 2D strain echocardiography (2DSE) data was available for subset of 65 subjects from the Finnish *MYBPC3* imaging study [24], of whom 20 were control subjects and 45 *MYBPC3*-Gln1061X variant carriers without (G+/LVH− $n = 18$) or with LVH (G+/LVH+ $n = 27$). The methodology of echocardiography and CMRI for the substudy has been previously published and is summarized in the Methods section of the

Supplementary material [24]. The G+/LVH+ patients were further divided into two groups according to HCM phenotype: mild ($n = 12$) and moderate ($n = 15$) HCM. Patients with moderate HCM were defined as having at least one of the following variables ≥ 75 th percentile of the HCM group: CMRI left ventricular maximal wall thickness (75th percentile limit ≥ 25 mm), echocardiographic global longitudinal strain ($\geq -13\%$), or CMRI measured degree of late gadolinium enhancement (LGE $\geq 22\%$ of the LV mass). Mild HCM was defined as not fulfilling any of these criteria.

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages, and continuous variables as means and standard deviations or medians followed by inter-quartile ranges. Differences between groups were analyzed using the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney or Kruskal-Wallis test for continuous variables. Binary logistic regression analysis with sex and age adjustment was used to confirm the validity of the novel ECG parameters RV1<RV2>RV3 and septal remodeling. The correlation of the extent of ECG pathology as absolute number of findings to imaging and laboratory parameters in the imaging substudy was analyzed with Spearman rank correlation. A two-tailed p-value of <0.05 was considered statistically significant for all tests. All calculations were performed with the SPSS software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, IBM Corp.).

Results

Baseline

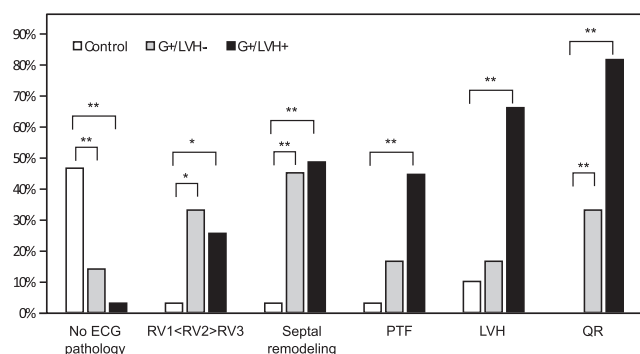
The baseline characteristics and conventional echocardiography findings of the three study groups are presented in Table 1 and Fig. 2A. There were more male subjects in the G+/LVH+ group

compared to the control and G+/LVH− group. The subjects in G+/LVH+ group were also older compared to the G+/LVH− group (48 ± 14 vs 33 ± 15 years, $p < 0.001$). The majority of the HCM patients were asymptomatic (78%). By definition, the G+/LVH+ group had significantly greater maximal wall thickness. The groups were balanced regarding left ventricular dimensions and ejection fraction. Left ventricular outflow tract obstruction was present at rest in 5 (5%) of HCM patients (a gradient of >30 mm Hg). The majority of G+/LVH+ patients had asymmetric septal hypertrophy (90%). Eight (8%) of the HCM patients had MWT in the lateral wall and one patient had posterior and another patient concentric hypertrophy. Two patients had MWT in the apical segments but also exhibited significant thickening of the whole septal wall and did not represent true apical hypertrophy. No differences in echocardiographic measurements were found between the G+/LVH− and control groups.

ECG

The ECG pathology findings are summarized in Table 2. There were 14 subjects (47%) in the control group with no ECG pathology in comparison to 6 (14%) and 3 (3%) in the G+/LVH− and G+/LVH+ groups, respectively ($p < 0.001$). Thus the finding of a completely normal ECG was uncommon in all mutation carriers including G+/LVH− subjects. The median number of ECG pathology was 1 (range 0–6) in the G+/LVH− and 5 (0–9) in the G+/LVH+ groups. A normal ECG with no identified pathology had a sensitivity of 47% and a specificity of 96% to discern control subjects from HCM mutation carriers. Q waves and repolarization abnormalities (QR) were common findings in the G+/LVH+ group. The presence of Q waves, ST depression and T-wave inversion was marked also in the G+/LVH− group (33%). ST depressions were associated with inverted T waves in 34/50 (68%) of the G+/LVH+ patients. Conventional ECG parameters of hypertrophy (Sokolow-Lyon and Cornell criteria) identified true LVH quite modestly in the G+/LVH+ group. The presence of P-terminal force, was a

A Distribution of ECG pathology in all subjects ($n = 170$)



B Distribution of ECG pathology in mutation carriers ($n = 140$)

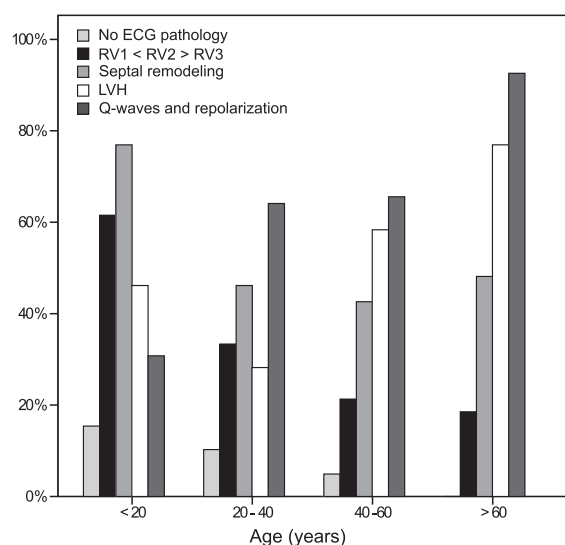


Fig. 2. Distribution of ECG pathology in A) all subjects ($n = 170$), * = $p < 0.05$ and ** = $p < 0.001$ for difference between indicated group and control group; B) in the mutation carriers (G+/LVH+ and LVH−, $n = 140$) stratified by age group. LVH = LV hypertrophy by any used criteria: Sokolow-Lyon criteria, Cornell voltage-duration product or Romhilt-Estes point score, QR = Q waves and repolarization abnormalities.

Table 2
ECG characteristics of the study groups.

	Control ($n = 30$)	G+/LVH− ($n = 42$)	G+/LVH+ ($n = 98$)	p-Value
ECG pathology	1 (0–4)	1 (0–6)	5 (0–9)*,†	<0.001
No ECG pathology	47% (14)	14% (6)*	3% (3)*,†	<0.001
Major criteria	3% (1)	36% (15)*	90% (88)*,†	<0.001
Q waves and repolarization	0	33% (14)*	82% (80)*,†	<0.001
Q waves	0	21% (9)*	38% (37)*	<0.001
Q V2–V6		7% (3)	15% (15)	0.031
Q II, III, aVF		10% (4)	16% (16)	0.035
Q I, aVL		2% (1)	16% (16)	0.004
ST depression	0	7% (3)	51% (50)*,†	<0.001
T-wave inversion	0	2% (1)	44% (43)*,†	<0.001
Prolonged QTc	0	7% (3)	18% (18)*	0.006
Absent Q V5–6	7% (2)	12% (5)	15% (15)	0.539
Giant T-waves	10% (3)	17% (7)	6% (6)	0.179
Novel ECG criteria				
RV1<RV2>RV3	3% (1)	33% (14)*	26% (25)*	0.005
Septal remodeling	3% (1)	45% (19)*	49% (48)*	<0.001
Maximal R-wave not in V4–6	7% (2)	19% (8)	23% (23)	0.122
Hypertrophy	10% (3)	17% (7)	66% (65)*,†	<0.001
Sokolow-Lyon criteria	10% (3)	2% (1)	15% (15)	0.079
Cornell criteria	0	7% (3)	40% (39)*,†	<0.001
Romhilt-Estes score ≥ 4	3% (1)	14% (6)	55% (54)*,†	<0.001
Other ECG features				
P-terminal force	3% (1)	17% (7)	45% (44)*,†	<0.001
QRS >100 ms	0	5% (2)	22% (22)*,†	<0.001
Fragmented QRS	27% (8)	21% (9)	46% (45)*	0.011
Prolonged PQ	0	2% (1)	11% (11)	0.032
Axis deviation	3% (1)	19% (8)	1% (1)*	0.002

ECG pathology presented as median and range in parentheses. All other variables presented as percentage and number of patients in parentheses.

* $p < 0.05$ for difference between indicated group and control group.

† $p < 0.05$ for difference between G+/LVH+ and G+/LVH− groups.

common finding in HCM patients and also present in 17% of G+/LVH– subjects. No significant differences between the groups were observed in the following parameters (not shown in the table): RI + SIII > 25 mm, RI + SIII–RIII–SI > 17 mm, S > RV4, PRWP, reverse R-wave progression in leads V1–V3.

The novel ECG criteria of RV1<RV2>RV3 (Fig. 1) and septal remodeling were significantly more common in mutation carriers without LVH than in control subjects (33% vs 3%, $p = 0.006$ and 45% vs 3%, $p < 0.001$, respectively) and in G+/LVH+ subjects compared with control subjects (26% vs 3%, $p = 0.015$ and 49% vs 3%, $p < 0.001$, respectively). In univariate binary logistic regression, with age and sex as covariates, both RV1<RV2>RV3 and septal remodeling retained their statistical significance (OR = 13.3, $p = 0.018$ for RV1<RV2>RV3 and OR = 21.8, $p = 0.004$ for septal remodeling).

Fig. 2B illustrates the different ECG findings stratified by age groups in the mutation carriers with and without LVH (G+, $n = 140$). RV1<RV2>RV3 and septal remodeling were more prevalent in younger subjects and, in contrast, the ECG findings of hypertrophy and QR were more pronounced in the older age groups.

Imaging substudy

The baseline characteristics of the imaging substudy groups are presented in Supplementary Tables 1 and 2. CMRI derived ejection fraction and LV end diastolic volume were normal in all study groups. Typical imaging findings in subjects with mild and moderate HCM were increased septal and maximal wall thickness, increased CMRI LV mass, reduced diastolic function and global longitudinal strain (GLS), and presence of LGE that increased with advanced disease. The prevalence of RV1<RV2>RV3, septal remodeling and other key pathologic ECG features according to HCM phenotype are illustrated in Fig. 3. RV1<RV2>RV3 was more prevalent in G+/LVH– and mutation carriers with mild LVH than in patients with moderate or severe HCM. Other ECG findings were more prevalent in the moderate HCM group compared to the mild HCM and G+/LVH– groups. No significant correlations of the novel ECG parameters RV1<RV2>RV3 and septal remodeling to imaging findings related to the septum or distribution of wall thickness in segmental strain, LGE or MWT values were found. The correlations of the extent of ECG pathology (0–15) to imaging and laboratory variables in gene mutation carriers with and without LVH are presented in Table 3, showing strong association with E/Em, GLS,

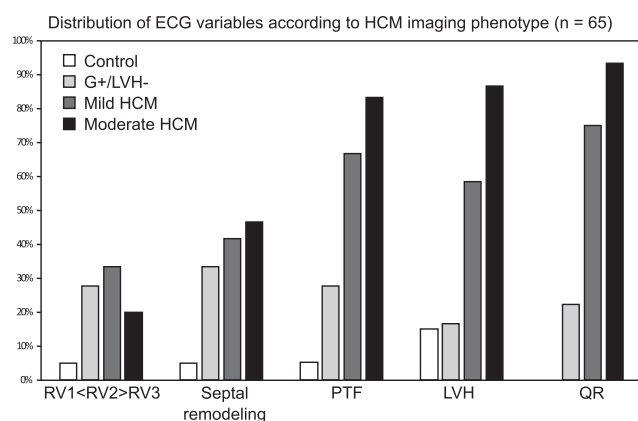


Fig. 3. Distribution of ECG variables according to HCM geno- and phenotype in the imaging substudy subjects ($n = 65$): Control, G+/LVH–, G+/Mild HCM, G+/Moderate HCM. Moderate HCM determined as MWT and/or GLS and/or LGE ≥ 75 th percentile and mild HCM as not fulfilling these criteria. RV1<RV2>RV3 is more prevalent in LVH– and mild HCM subjects whereas presence of septal remodeling increases with changes related to HCM. LVH = LV hypertrophy by any used criteria: Sokolow-Lyon criteria, Cornell voltage-duration product or Romhilt-Estes point score, PTF = P-terminal force ≥ 0.04 mm·s, QR = Q waves and repolarization abnormalities.

Table 3

Correlation of variables to the extent of ECG pathology.

Variable	ECG pathology	
	ρ	P
ECHO E/E'	0.58	<0.001
ECHO global systolic longitudinal strain	0.56	<0.001
ECHO mechanical dispersion	0.58	<0.001
CMRI LGE extent	0.62	<0.001
CMRI LV mass index	0.58	<0.001
CMRI maximal wall thickness	0.76	<0.001
NT-proBNP	0.62	<0.001

Spearman rank correlation of echocardiographic (ECHO) and cardiac magnetic resonance imaging (CMRI) variables and NT-proBNP to the extent of ECG pathology in subjects with the HCM-causing variant (0–15). LGE = late gadolinium enhancement.

mechanical dispersion, LGE, LV mass index, MWT, and levels of circulating NT-proBNP.

The ECG finding of QR had good sensitivity (95%) and relatively good specificity (84%) for the presence of LGE (95% of patients with LGE had QR compared to 16% of patients without LGE, $p < 0.001$ for Fisher's exact test). There were no significant correlations between the localization of LGE and localized ECG-findings such as Q waves or T-wave inversion in the anterior or inferior leads.

The ability of ECG findings to differentiate between study groups

Table 4 shows the diagnostic value of ECG parameters and their combination for differentiating mutation carriers with and without LVH from the control subjects. The major ECG criteria [22] performed well in differentiating G+/LVH+ patients from control subjects, with a sensitivity of 90% and specificity of 97%. The novel parameters of RV1<RV2>RV3 and septal remodeling did not improve the diagnostic sensitivity of the previously proposed criteria in differentiating G+/LVH+ patients from control subjects. Conventional variables such as the major criteria or QR had modest sensitivity to differentiate between G+/LVH– and control subjects. In contrast, RV1<RV2>RV3 and septal remodeling both had incremental value in the identification of mutation carriers without LVH. When used in conjunction with QR the sensitivity was 52% and 64%, respectively, with a specificity of 97%.

Discussion

The main findings of this study are: 1) a normal ECG is rare (3%) in HCM patients with *TPM1*-Asp175Asn or *MYBPC3*-Gln1061X variants in a comprehensive ECG analysis; 2) a normal ECG is also uncommon (14%) in G+/LVH– subjects; 3) the extent of ECG pathology correlates with severity of the HCM phenotype; 4) novel ECG parameters RV1<RV2>RV3 and septal remodeling were very specific to carriers of

Table 4

Effectiveness of ECG variables to separate G+/LVH+ and G+/LVH– groups from the control group.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
G+/LVH+ ($n = 98$)				
Major criteria (≥ 1)	90%	97%	99%	74%
QR	82%	100%	100%	63%
RV1<RV2>RV3	26%	97%	96%	28%
Septal remodeling	49%	97%	98%	37%
G+/LVH– ($n = 42$)				
Major criteria (≥ 1)	36%	97%	94%	52%
QR	33%	100%	100%	52%
RV1<RV2>RV3	33%	97%	93%	51%
RV1<RV2>RV3 and/or QR	52%	97%	96%	59%
Septal remodeling	45%	97%	95%	56%
Septal remodeling and/or QR	64%	97%	96%	66%

NPV = negative predictive value, PPV = positive predictive value, QR = Q waves and repolarization abnormalities.

pathogenic variants with and without LVH and 5) these novel parameters with the combination of Q waves and repolarization abnormalities exhibited good sensitivity and excellent specificity to differentiate the G+/LVH— group from the control group.

Study findings in the context of current literature

The novel ECG criteria RV1<RV2>RV3 and septal remodeling proposed in this study have good specificity to differentiate between carriers of pathogenic variants for HCM and the control group. Previous reports on the ECG findings of G+/LVH— subjects have been varied and longitudinal follow-up data is scarce [7,8,10]. Some smaller scale studies have reported Q waves and repolarization abnormalities [9], while in others there have been very limited ECG findings [7]. The largest published G+/LVH— cohort to date of 76 subjects with a number of different variants, reported Q waves and repolarization abnormalities in 25% of subjects, a finding that was a specific (98%) marker for young LVH— variant carriers (42% of subjects in the study were <18 years old) [8]. In the current study Q waves were present in 21% of G+/LVH— subjects compared with none in the control group.

Previously the low sensitivity and mostly limited specificity of ECG variables to differentiate G+/LVH— subjects from healthy control individuals has made their use in clinical practice challenging. In this study the combination of RV1<RV2>RV3 or septal remodeling with Q waves and repolarization abnormalities resulted in a significant improvement of the sensitivity of the ECG analysis to over 50% with a concurrent specificity of 97%. Application of the RV1<RV2>RV3 + QR criteria especially is relatively easy in clinical daily practice and could be used in the screening of HCM families.

According to our study, ECG criteria for HCM identified pathogenic variant carriers with LVH with high sensitivity, specificity and positive likelihood ratio and compared well to a previous study with a similar age distribution [10]. The extent of ECG pathology and degree of hypertrophy and dysfunction of the left ventricle correlated with the extent of ECG pathology, which corroborates a previous finding [25]. We also found that GLS, a sensitive marker of LV dysfunction, and NT-proBNP, an established marker of disease severity and prognosis in HCM, both correlate strongly to the extent of ECG pathology. These findings are of importance in the clinical follow-up of HCM patients, as the ECG is an inexpensive and reproducible test.

In our study, the Sokolow-Lyon criteria performed suboptimally in identifying LVH, with only 15% fulfilling the criteria in the G+/LVH+ group and 10% in the control group. The Cornell criteria were positive in 40% and the Romhilt-Estes score in 55% of the hypertrophic patients – results that were in line with previous studies [26]. None of the LVH criteria differed significantly in prevalence between the G+/LVH— and control groups.

Possible pathophysiological mechanisms

The novel ECG parameter proposed in this study, the RV1<RV2>RV3 sign, represents a disorderly distribution of the maximal R-wave amplitudes in leads V1–V3. Normally the R-wave amplitude increases from V1 to V3. Although not specifically reported, previous publications have shown subjects with the RV1<RV2>RV3 pattern – both HCM patients with LVH in the age range of 10 to 69 years [27,28] and in pathogenic variant carriers without echocardiographic ventricular hypertrophy [4,6].

The RV1<RV2>RV3 finding is more prevalent in young subjects (Fig. 2B) and in those with mild HCM (Fig. 3). It is possible that this reflects an early stage of the developing disease as a segmental structural change of the interventricular septum and is later substituted with other more pronounced ECG changes due to significant hypertrophy and fibrosis. However, even with comprehensive modern imaging echocardiographic and CMRI methods, we could not identify significant

correlation between the RV1<RV2>RV3 sign and characteristics of the interventricular septum of G+/LVH— subjects.

In our previous report, the presence of septal remodeling identified DCM patients either with the lamin A/C variant (82% prevalence) or no identified gene substrate (21%) compared to control subjects (0%) [23]. Thus it is not a specific finding for HCM and instead might reflect general LV remodeling of patients with cardiomyopathies of different etiologies. No clear correlation of the location of LGE to Q waves was found in this study reflecting the results of previous larger scale CMRI reports [12,25]. On the other hand, the presence of Q waves and repolarization abnormalities was significantly more prevalent in patients with LGE.

Limitations of the study

We studied carriers of two different pathogenic variants of HCM: MYBPC3-Gln1061X and TPM1-Asp175Asn. Both are prevalent in the Finnish HCM population and as such are probably similar to other pathogenic MYBPC3 and TPM1 variants causing HCM. Therefore, we would presume that the results are generalizable to the spectrum of carriers of pathogenic variants in these two genes. The results of this study have to interpret with caution when discussing the diagnostics and screening of families without a known pathogenic variant. The imaging subset sample size was limited and included only subjects with the MYBPC3-Gln1061X variant. Thus, the results of the imaging study have to be interpreted with caution.

Conclusions

Our study shows that G+/LVH+ patients can be identified with high sensitivity, specificity and predictive values. Conventional ECG was also valuable in the identification of G+/LVH— subjects from control subjects using the novel ECG parameters of RV1<RV2>RV3 and septal remodeling in combination with Q waves and repolarization abnormalities. This finding needs to be further evaluated in larger patient cohorts, but holds promise as a clinically feasible tool to identify subjects with preclinical changes of HCM and aid in the screening and follow-up of relatives of HCM patients.

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Disclosure of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jelectrocard.2018.07.009>.

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